COMPARISON OF THE DIAGNOSTIC VALUES OF GD-EOB-DTPA AND GD-DTPA FOR HEPATOCELLULAR CARCINOMA ASSOCIATED WITH HEPATITIS B CIRRHOSIS

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ABSTRACT

Objective*: To explore the diagnostic value of Gd-EOB-DTPA MRI for hepatocellular carcinoma (HCC) associated with hepatitis B cirrhosis.*

Methods*: A total of 32 hepatitis B cirrhosis patients with 34 HCC lesions underwent two MRIs (mode 1: T2WI, DWI, T1WI in-phase and opposed-phase and dynamic Gd-DTPA enhancement (native phase, arterial phase, portal-venous phase and delayed phase); mode 2: T2WI, DWI, T1WI in-phase and opposed-phase and dynamic Gd-EOB-DTPA enhancement (native phase, arterial phase, portal-venous phase, delayed phase and hepatobiliary phase). The images were analyzed by two readers with double blind method. The signal characteristic of all lesions, the enhancement modes, and the confidence scores of two readers were recorded. The confidence scores, consistency, areas under the receiver operating characteristic (ROC) curve, sensitivity and positive predictive values (PPV) of two readers in diagnosing the hepatocellular carcinoma were compared between two imaging modes.*

Results*: ① The confidence scores of two readers in diagnosing the hepatocellular carcinoma under the second imaging mode were higher than those under the first imaging mode, and the differences were statistically significant (P<0.05). The consistency of two readers in diagnosing the hepatocellular carcinoma under the second imaging mode was also increased. ② The areas under the ROC curve of two readers in diagnosing the hepatocellular carcinoma under the second imaging mode were increased compared with those under the first imaging mode, and the differences were statistically significant (P<0.05). ③ The sensitivities of two readers in diagnosing the hepatocellular carcinoma under the second imaging mode were higher than those under the first imaging mode, and the differences were statistically significant (P<0.05). There were no significant differences in PPV of two readers between two imaging modes (P>0.05).*

Conclusion*: Gd-EOB-DTPA MRI may improve the diagnostic confidences of readers on HCC associated with hepatitis B cirrhosis and thus increase the diagnostic efficacy.*

Keywords: *Liver diseases, Liver tumors, Magnetic resonance imaging, Gd-DTPA, Gd-EOB-DTPA.*

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in China. Especially, the advanced HCC has a poor prognosis, and its mortality rate has risen to the second place in all cancers. Early detection and diagnosis are an important way to improve the survival rate of HCC patients. At present, the ultrasound (US), CT and MRI are the most commonly used methods to detect and diagnose HCC associated with hepatitis B cirrhosis, and each has its advantages. In particular, the dynamic contrast-enhanced MR scanning plays an important role in the detection and qualitative diagnosis of HCC[(1)]. Some studies abroad showed that the efficacy of multiphase dynamic contrast-enhanced MRI using the liver specific contrast agent GD-EOB-DTPA (gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid) in the diagnosis of hepatocellular carcinoma, especially small hepatocellular carcinoma is superior to that of the dynamic contrast-enhanced MDCT[(2-4)]. However,

there are few reports on comparison of the diagnostic efficacies of GD-ETP-DTPA and GD-DTPA (MR conventional contrast agent) contrast-enhanced MRIs. We retrospectively analyzed 34 HCC lesions in 32 patients with liver cirrhosis and discussed the diagnostic value of GD-EOB-DTPA dynamic contrast-enhanced MRI for HCC.

Materials and methods

Clinical data

This retrospective study was approved by the Ethics Committee of Nantong Third People's Hospital, and the patients' informed consent was waived. General information: From January 2017 to March 2020, a total of 32 patients were included in the study, including 23 males and 9 females. The patients aged 32-74 years, with an average age of (53.78 ± 10.15) years and a median age of 52 years .The interval time between two dynamic contrast enhanced-MRI examinations was 3-7 days. A total of 34 HCC lesions were found. Of which, 25 HCC lesions in 25 patients were confirmed by the pathologic examinations after surgical resections; 6 HCC lesions in 4 patients were confirmed by tumor staining and lipiodol deposition during interventional therapy. 3 HCC lesions in 3 patients were confirmed by clinical manifestations and typical imaging findings.

Inclusion criteria: ① The patients with hepatitis B cirrhosis had liver space occupying lesions indicated by ultrasound or CT. ② The patients underwent two dynamic contrast enhanced-MRI examinations using GD-EOB-DTPA and GD-DTPA, respectively within 7 days. ③ The intrahepatic lesions in the patients were confirmed as HCC. ④ The patients did not undergo liver surgery or interventional therapy before examination.

MR contrast agent and injection methods

① GD-EOB-DTPA (Primovist, Bayersehering Pharma, Berlin, Germany), is produced by Bayer AG, a German chemical and pharmaceutical company. 10ml GD-EOB-DTPA was preloaded into a syringe. The specific application method: the bolus injection of GD-EOB-DTPA into the peripheral elbow vein was performed with a dose of 0.1 ml / kg body weight at an injection rate of 1.0-1.5 ml / s. Immediately after the injection, the catheter was flushed with 20 ml of physiological saline at a rate of 2 ml / s. ② GD-DTPA: preparation specification: 15ml / bottle, it was used with a dose of 0.2ml / kg body weight and an injection rate of 2.0-2.5ml / s, and the catheter was flushed with 20 ml of physiological saline at a rate of 2 ml / s immediately after the injection.

MRI scanning technology

GE 1.5T HDE magnetic resonance scanner was used. The scan sequence and parameters were as follows: respiratory triggering in axial plane FSE T2WI + FS, TR = 2 respiratory cycles, TE = 90 ± 10 ms, slice thickness 5 mm, slice spacing 1.0 mm, FOV 35 cm × 30 cm, matrix 320 × 224, NEX 2.00; single-shot SE-EPI DWI, TR5200 ms, TE73.40 ms, slice thickness 5 mm, layer spacing 1.0 mm, FOV35 cm×40 cm, matrix 128 × 128, NEX 8.00; FSPGR T1WI in-phase and opposed-phase imaging; TR=130-250 ms, TE 2.25/4.5 ms, slice thickness 5 mm, slice spacing 1.0 mm, FOV36 cm×36 cm, matrix 256×170, NEX 1.00; LAVA enhancing 3-D scanning, arterial phase 19-22s, portal venous phase 55-60s, equilibrium phase 180s, TR5.14 ms, TE2.30 ms, slice thickness 5 mm, layer spacing 2.50 mm, FOV40 cm×36 cm, matrix 288×192. According to the liver sizes, single-phase whole liver scanning was completed within 12-15s. The whole liver scanning was completed at 20 min after GD-EOB-DTPA was injected as contrast agent during hepatobiliary phase.

Image Analysis

Two experienced radiologists independently read the images in a PACS workstation. The images were divided into two groups, the first group included images obtained from dynamic Gd-DTPA contrast-enhanced MRI combined with T2WI, DWI and T1WI in-phase and opposed-phase, dynamic enhancement (native phase, arterial phase, portal-venous phase and delayed phase); the second group included images obtained from dynamic Gd-EOB-DTPA contrast-enhanced MRI combined with T2WI, DWI, T1WI in-phase and opposed-phase, dynamic enhancement (native phase, arterial phase, portal-venous phase, delayed phase and hepatobiliary phase). The readers evaluated all focal liver lesions, but the cysts and lesions larger than 5 cm were not included in the study. Lesions were scored according to image quality. The scores were as follows: 5 points for confirmed hepatocellular carcinoma, 4 points for possible hepatocellular carcinoma, 3 points for unconfirmed hepatocellular carcinoma, 2 points for possible non-hepatocellular carcinoma and 1 point for confirmed non-hepatocellular carcinoma, 0 point for the existed lesion which was not found. The susceptibility and positive predictive values were

calculated only for lesions with a score of 4 and 5 points.

Statistical analysis

SPSS 21.0 software package was used for statistical analysis. Comparison of confidence scores of two readers was performed using the paired t-test. Comparison of consistency between two readers was made using the Kappa test. Kappa value <0.40 indicated that the consistency was poorer; Kappa value 0.40-0.75 indicated that the consistency was moderate to high; Kappa value > 0.75 indicated that the consistency was excellent. ROC curve analysis was performed using MedCalc software, the areas under the curve (AUC) was compared using DeLong et al test. The sensitivities and positive predictive values were compared using a paired chi-square test (McNemar). P <0.05 indicated that the difference was statistically significant.

Results

Confidence scores and consistency of two readers in diagnosing the hepatocellular carcinoma under two imaging modes

The confidence scores of two readers in diagnosing the hepatocellular carcinoma under the second imaging mode were higher than those under the first imaging mode, and the differences were statistically significant (P<0.05). The consistency between two readers in diagnosing the hepatocellular carcinoma under the second imaging mode was also increased (Table 1).

Imaging mode	Confidence score		Kappa value
	Reader 1	Reader 2	
Gd-DTPA	3.94±0.736	3.88±0.769	0.674
Gd-EOB-DTPA	4.76±0.554	4.76±0.479	0.823
t	-7.668	-8.558	
p	0.000	0.000	

Table 1: The confidence scores of two readers in diagnosing the hepatocellular carcinoma.

The areas under the ROC curve of two readers in diagnosing the hepatocellular carcinoma under two imaging modes

The areas under the ROC curve of two readers in diagnosing the hepatocellular carcinoma under the second imaging modes were increased compared with those under the first imaging mode, an the differences were statistically significant (P<0.05); There was no statistical significant difference in the area under the ROC curve in diagnosing the hepatocellular carcinoma under the same imaging mode between two readers (P> 0.05) (Table 2).

Imaging mode	ROC area under the curve		Z	P
	Reader 1	Reader 2		
Gd-DTPA	0.903±0.046 (0.780-0.970)	0.900±0.048 (0.778-0.968)	0.094	0.925
Gd-EOB-DTPA	0.986±0.011 (0.900-1.000)	0.990±0.009 (0.906-1.000)	0.759	0.448
Z	2.193	2.182		
P	0.028	0.029		

Table 2: The areas under the ROC curve of two readers in diagnosing the hepatocellular carcinoma under two imaging modes (Mean±SD).

The sensitivities and PPV of two readers in diagnosing the hepatocellular carcinoma under two imaging modes

The sensitivities of two readers in diagnosing the hepatocellular carcinoma under the second imaging mode were higher than those under the first imaging mode, and the differences were statistically significant (P<0.05). There were no significant differences in PPV of two readers between two imaging modes (P>0.05) (Table 3).

Imaging mode	Reader 1		Reader 2	
	Sensitivity	PPV	Sensitivity	PPV
Gd-DTPA	76.47 (58.8-89.3)	96.3 (80.6-99.9)	70.59 (52.5-84.9)	96.0 (79.1-99.9)
Gd-EOB-DTPA	94.12 (80.3-99.3)	97.0 (83.9-99.9)	97.06 (84.7-99.9)	97.1 (84.4-99.9)
P	0.031	1.000	0.004	1.000

Table 3: The sensitivities and PPV of two readers in diagnosing the hepatocellular carcinoma under two imaging modes.

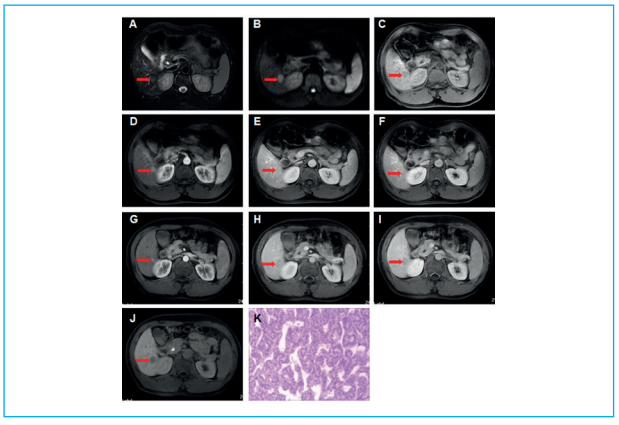

Figure 1: Small hepatocellular carcinoma in lower segment of right posterior lobe of liver. **A**: The lesion showed a slightly higher signal (arrow)on T2WI. **B**: The lesion showed a significantly high signal (arrow) on DWI. **C**: The lesion showed a slightly lower signal (arrow) on T1 with fat saturation. ***D***: A significantly enhanced lesion (arrow) was showed in the arterial phase (Gd-DTPA). **E**, **F**: The lesion with a equal signal was showed unclearly (arrow)in the portal venous phase and delayed phase (Gd-DTPA). **G**: A significantly enhanced lesion (arrow) was showed in the arterial phase (Gd-EOB-DTPA). **H-J**: The lesion with a low signal intensity was showed in the portal venous phase, 3 minutes delayed phase and 20 minutes delayed phase, and the boundaries were clear (arrow). **K**: The pathology confirmed that the lesion was a moderately or poorly differentiated hepatocellular carcinoma.

Among 34 lesions of the hepatocellular carcinomas, reader 1 discovered 7 unconfirmed lesions and had 1 misdiagnosis under the first imaging mode, corrected the diagnoses of 6 lesions under the second imaging mode; reader 2 discovered 9 unconfirmed lesions and had 1 misdiagnosis under the first imaging mode and corrected the diagnoses of 9 lesions under the second imaging mode (Figure.1, 2).

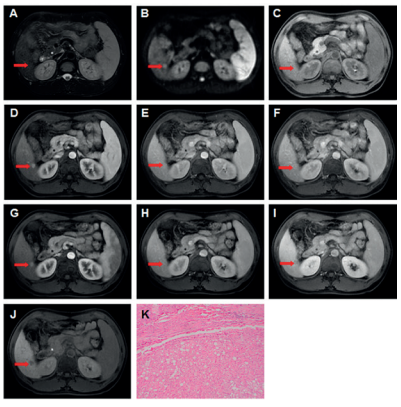

Figure 2: Small hepatocellular carcinoma in lower segment of right posterior lobe of liver. **A**: The lesion showed an equal signal on T2WI (arrow). **B**: The lesion showed a high signal on DWI (arrow). **C**: The lesion showed an equal signal on T1 with fat saturation (arrow). **D**: A significantly enhanced lesion (arrow) was showed in the arterial phase (Gd-DTPA). **E, F**: The equal signal of the was showed unclearly (arrow)in the portal venous phase and delayed phase (Gd-DTPA). **G**: A significantly enhanced lesion (arrow) was showed in the arterial phase (Gd-EOB-DTPA). **H**: The lesion with equal signal was showed in the portal venous phase. **I-J**: The lesion with a low signal was showed in 3 minutes delayed phase and 20 minutes delayed phase, and the boundaries were clear (arrow). **K**: The pathology confirmed that the lesion was a moderately differentiated hepatocellular carcinoma.

Discussion

As we all know, a typical HCC shows a high signal on T2WI and DWI, and "rapid increase and decrease "enhancement pattern is demonstrated after dynamic enhancement[5]. But a small part of the HCCs show an equal or high signal in the delayed phase, the reasons for this : ① the blood flow in patient with liver cirrhosis is slow, the contrast agent content in the hepatic artery is still higher in the delayed phase, and the lesion still shows a high signal; ② the portal vein participates in the blood supply of the lesion, and the retention time of the contrast agent is longer, the lesion is continuously enhanced and thus shows a show a high signal in the delayed phase; ③ the inaccurate scan delay time or other technical reasons lead to that the lesion shows a high signal in the delayed phase. This makes it difficult to diagnose the nontypical small HCC associated with hepatitis B cirrhosis.

Gd-EOB-DTPA is a new bifunctional specific hepatobiliary contrast agent, and it not only has the characteristics of extracellular contrast agent, but also can be specifically taken in by the liver cells in the hepatobiliary phase. Therefore, it can increase the detection rate of the focal liver lesions, especially the focal liver lesions less than 1cm and provide a basis for qualitative diagnosis of liver lesions. On the one hand, GD-EOB-DTPA has the same characteristics as conventional MRI contrast agent GD-DTPA, it is firstly distributed in the extracellular space after the injection; on the other hand, the EOB of molecular structure of GD-EOB-DTPA can be combined with the plasma proteins at about 10-20min after injection, and then is absorbed selectively and specifically by the liver cells through the organic anion transport system and excreted through the biliary system. Therefore, GD-EOB-DTPA is mainly distributed in the blood vessels and hepatobiliary system after intravenous injection.

Gd-EOB-DTPA dynamic contrast-enhanced MRI of the liver can be divided into dynamic phase and hepatobiliary phase, the dynamic phase starts from injection of contrast agent to 30-180 seconds after injection, the enhancement pattern of the liver during this phase is similar to GD-DTPA dynamic enhancement, and the peak contrast enhancement is achieved within about 60-70 seconds[6]; the hepatobiliary phase starts at 20 minutes after injection of contrast agent, the contrast agent is being absorbed by the normal liver cells during this phase, so that the normal liver parenchyma demonstrates highly homogeneous enhancement, the lesion without normal liver cells shows a low signal, but actually GD-EOB-DTPA dynamic phase is not exactly the same with GD-DTPA dynamic enhancement. Firstly, compared with GD-DTPA dynamic enhancement, the enhancement of HCC in Gd-EOB-DTPA arterial phase is relatively weak; secondly, although it is considered in some literatures that the images obtained from portal venous phase and delayed phase of Gd-EOB-DTPA-enhanced MRI are comparable with those obtained from GD-DTPA dynamic contrast enhancement during the corresponding phases[7,8], we consider that the images obtained by these two contrast agents during the same phases are not fully equivalent. Studies[9-10] have shown that the main effects of Gd-EOB-DTPA

for patients with HBV-related liver cirrhosis are to assess liver cirrhosis tubercle, increase the detection rate of nodular lesions and provide differential diagnosis information of early HCC and liver cirrhosis tubercle.

This study showed that the multi-phase dynamic Gd-EOB-DTPA-enhanced MRI increased the sensitivities and confidence scores of two readers in diagnosing HCC compared with the dynamic GD-DTPA enhanced MRI, and the differences were statistically significant ($P<0.05$), and the consistency of two readers in diagnosing the hepatocellular carcinoma under the mode of Gd-EOB-DTPA enhanced MRI was increased. After Gd-DTPA dynamic enhancement, 6 of the 34 HCC showed equal or slightly higher signals in the delayed phase, no typical enhancement pattern of rapid increase and decrease was demonstrated, this brought certain difficulties in diagnosis. But after GD-EOB-DTPA dynamic enhancement, 4 lesions showed typical HCC enhancement mode, 6 lesions showed low signals in the hepatobiliary phase, thereby greatly improving confidence in diagnosing HCC. The reason is that after GD-EOB-DTPA enhancement, the normal liver cells specifically absorb contrast agent in the 3 minutes delayed phase and hepatobiliary phase, the hepatic parenchyma hepatic signal is highest especially in the hepatobiliary phase[11], while HCC does not contain normal liver cells, and thus cannot specifically absorb GD-EOB-DTPA; the difference in signal intensity between lesion and normal liver parenchyma is maximal, and the absolute value of lesions-liver contrast to noise ratio (CNR) is the highest among all phases; therefore, the lesion is showed more clearly in this phase than in other phases, so GD-EOB-DTPA enhanced dynamic MRI increases the confidence in diagnosing HCC compared with Gd-DTPA dynamic enhancement.

In addition, there are some limitations in this study, which mainly demonstrates that not all of HCC were confirmed by surgical pathology. In this study, 25/34 (73.5%) HCC lesions were confirmed by surgical pathology, 9 HCC lesions were confirmed through tumor staining and lipiodol deposition in interventional therapy or typical imaging findings.

Conclusions

In summary, Gd-EOB-DTPA multi-phase dynamic contrast-enhanced scanning, especially the images obtained in the hepatobiliary phase improve the lesion-liver CNR, and thus improve the confidences and sensitivities of different readers in diagnosing HCC associated with hepatitis B cirrhosis.

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Ethics approval
This retrospective study was approved by the Ethics Committee of Nantong Third People's Hospital, and the patients' informed consent was waived.

Authors' Contributions
Conceived and designed the experiments: WC JL. Performed the experiments: XZ AF. Analyzed the data: TZ. Wrote the paper: TZ JL.

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